Original Article

Effect of cortisol and glycosylated-hemoglobin levels on mortality in intensive care unit

Oznur Sen, MD, Ugur Uzun, MD, Nurdan Aydin, MD, Isil Guldogan, MD.

ABSTRACT

الأهداف: في دراستنا، بحثنا في آثار مستويات الكورتيزول في الدم والهيموجلوبين الغليكوزيلاتي على معدل الوفيات لدى المرضى المقبولين في وحدة العناية المركزة وما إذا كان يمكن استخدام هذه العوامل كمؤشرات موثوقة لتقييم مخاطر الوفيات لدى هؤلاء المرضى.

المنهجية: وبعد الحصول على موافقة لجنة الأخلاقيات، اشتملت الدراسة على 79 مريضًا تم قبولهم في وحدة العناية المركزة في الدراسة. من ملفات المرضى قمنا بجمع بيانات عن التركيبة السكانية (العمر والجنس) ووجود داء السكري ومستويات الكورتيزول والهيموجلوبين الغليكوزيلاتي والجلوكوز واللاكتات التي تم قياسها أثناء العلاج في المستشفى، إلى جانب درجات علم وظائف الأعضاء الحاد والتقييم الصحي المزمن (APACHE II) المحسوبة ضمن أول 24 ساعة. في دراستنا، خططنا لدراسة العلاقة بين مستويات الكورتيزول والهيموجلوبين الغليكوزيلاتي ومعدل الوفيات لدى المرضى.

النتائج: اشتملت الدراسة على 79 مريضا في الدراسة. كان معدل وفيات المرضى المشمولين في الدراسة 65.8%. في النموذج الذي تم وضعه مع جميع المتغيرات، حددنا مستوى الكورتيزول (p=0.017) ودرجات علم وظائف الأعضاء الحاد والتقييم الصحي المزمن (p=0.005) (APACHE II) كعوامل مؤثرة على معدل الوفيات.

الخلاصة: وجد أن مستويات الكورتيزول في وقت القبول في وحدة العناية المركزة تؤثر على معدل الوفيات ويمكن اعتبارها عاملاً تنبؤيًا، في حين لم تظهر مستويات الهيموجلوبين الغليكوزيلاتي أي تأثير من هذا القبيل. كما تشير النتائج التي توصلنا إليها إلى أن مستويات الكورتيزول والهيموجلوبين الغليكوزيلاتي لم يكن لها تأثير على مدة التهوية الميكانيكية أو مدة الإقامة في وحدة العناية المركزة.

Objectives: To research the effects of blood cortisol and hemoglobinA1c (HBA1C) levels on mortality in patients admitted to the intensive care unit (ICU) and whether these factors could be used as reliable indicators for mortality risk assessment in these patients.

Methods: After receiving approval from the ethics committee, 79 patients admitted to ICU were included in the study. From patient files, we collected data on demographics (age, gender), presence of diabetes mellitus, and levels of cortisol, HbA1C, glucose, and lactate measured during hospitalization, along with acute physiology and chronic health evaluation (APACHE) II scores calculated within the first 24 hours. In our study, we planned to investigate the relationship between patients' cortisol and HbA1C levels and mortality.

Results: A total of 79 patients were included in the study. The mortality rate of the patients included in the study was 65.8%. In the model established with all variables, only cortisol level (p=0.017) and APACHE II score (p=0.005) were defined to affect mortality.

Conclusion: Cortisol levels at the time of admission to the ICU were found to affect mortality and can be considered a predictive factor, while HBA1C levels showed no such effect. Our findings indicate that neither cortisol nor HBA1C levels had an impact on the duration of mechanical ventilation or length of stay in the ICU.

Keywords: glycated hemoglobin, intensive care units, mortality, steroids

Saudi Med J 2024; Vol. 45 (5): 476-480
doi: 10.15537/smj.2024.45.5.20240076

From the Department of Anesthesiology and Reanimation Unit (Sen, Aydin), SBU Haseki Training and Research Hospital, Istanbul; and From the Department of Anesthesiology and Reanimation Unit (Uzun, Guldogan), SBU Tepecik Training and Research Hospital, İzmir, Turkey.

Received 31st January 2024. Accepted 21st April 2024.

Address correspondence and reprint request to: Dr. Oznur Sen, Department of Anesthesiology and Reanimation. SBU Haseki Training and Research Hospital, Istanbul, Turkey. E-mail: senoznur@gmail.com ORCID ID: https://orcid.org/0000-0002-4644-6978

Cortisol is secreted from the adrenal cortex under the influence of adrenocorticotropic hormone (ACTH) diurnally or in response to stress. It increases the risk of hyperglycemia by stimulating gluconeogenesis in the liver, reducing glucose uptake in adipose tissue and skeletal muscles, suppressing insulin secretion, and causing insulin resistance and inflammation.[1] Effective control of hyperglycemia directly reduce mortality and morbidity.[2] Many studies have examined the effect of cortisol levels and blood sugar regulation on intensive care mortality and morbidity in patients followed up in the intensive care unit (ICU).[3,4] However, studies examining the effects of blood cortisol levels before admission to the ICU and glycosylated hemoglobin (HBA1C) levels, which reflect blood sugar regulation over the last 2-3 months, on morbidity and mortality in the ICU are scarce.

This study aim to research how HBA1C and cortisol levels affect the mortality of patients admitted to the ICU and their potential as predictors of mortality.

Methods. A total of 79 adult patients, 42 women and 37 men, who were admitted to ICU between January 2022 and February 2023 were included in our study. We excluded patients under the age of 18, those admitted for postoperative care, and steroid users from the study, as these factors could distort HBA1C and cortisol levels. We recorded demographic information (age and gender) and the presence of diabetes from patient files. Patients whose cortisol, HBA1C, glucose, and lactate levels were checked within the first hour of admission to the ICU and whose APACHE II scores were calculated within the first 24 hours were included in the study. We conducted high liquid chromatography using a Bio-Rad Variant II (Bio-Rad Laboratories, Hercules, CA, USA) device to measure HBA1C levels, and cortisol levels were assessed with a DxI immunoanalyzer (Beckman Coulter Inc., CA, USA). HBA1C levels were expressed as percentages (%), and cortisol levels were given in g/dl.

The primary endpoint of the study was the patient's mortality in the ICU, and the secondary endpoint measure was the number of days spent on mechanical ventilation and in the ICU. The APACHE II score, computed in the first 24 hours for the included patients, was used as an indicator of disease severity.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

To identify prior research related to the impact of cortisol and glycosylated-hemoglobin levels on mortality in ICU settings, Several electronic databases, including Web of Science, Scopus, and PubMed were used for a comprehensive literature search. The search plan used a combination of keywords and MeSH terms tailored to capture the broadest spectrum of relevant studies. These terms included "cortisol," "glycosylated hemoglobin," "HbA1c," "mortality," "intensive care unit," and "critical care" among others, both singly and in various combinations. Both observational and interventional studies were considered for inclusion. Ethics committee approval numbered 216/2023 was received from Health Sciences University Haseki Training and Research Hospital. This is retrospective cross-sectional clinical trial. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Statistical analysis. Normality control of numerical variables in the study was checked with the Kolmogorov-Smirnov test. As descriptive statistics, since the distribution of data for numerical variables was not normal, frequency (n) and percentage (%) were given for median (minimum-maximum) categorical variables. To determine whether there was a significant difference between patient mortality and discharge, the Mann-Whitney U test was used. Binary logistic regression analysis was used to examine the factors affecting mortality of the patient, and odds ratio and confidence intervals were given. Linear regression analysis was performed to examine the factors affecting the number of days spent in mechanical ventilator and ICU. The probability of type 1 error was taken as 0.05 in all analyses. The Statistical Package for the Social Sciences for Windows Version 22 (IBM Corp., Armonk, N.Y., USA) program was used in all analyses.

Results. A total of 79 patients were included in the study (Table 1). Of these, 29 patients were previously diagnosed with diabetes. The number of patients discharged from the ICU was 27, and that of patients who died was 52. Blood samples revealed a median HBA1C of 5.7% (4.30-11.60) and a median cortisol level of 20.49 (0.88-62.20) g/dl for all patients, while for the deceased patients, the mean HBA1C was 5.8 (4.80-11.50) and the mean cortisol level was 26.69 g/dl (7.98-62.20) (Table 2).

The mortality rate of the patients was 65.8%. In the model incorporating all variables, only the cortisol level (p=0.017) and APACHE II score (p=0.005) were defined as affecting mortality. It was seen that a one point increase in the APACHE II score enhanced

Table 1 - Demographic data of the patients included in the study

Characteristic	Value
Gender, n (%)	
Female	42 (53.2)
Male	37 (46.8)
Age (years) *	67 (19-96)
Mortality, n (%)	
Dead	52 (65.8%)
Discharged	27 (34.2%)
Day of stay in mechanical ventilator*	7 (0-119)
Day of stay in intensive care unit *	16 (2-120)
HBA1C (%)*	5.7 (4.30-11.60)
Cortisol (g/dl)*	20.49 (0.88-62.20)
Lactate (mmol/L)*	1.5 (0.40-8.40)
Blood Sugar (mg/dl)*	143 (42-421)
APACHE II*	21 (7-46)

*Median(min-max), APACHE: Acute Physiology And Chronic Health Evaluation

Table 2 - Laboratory data according to mortality status.

Group	HBA1C	Cortisol	Lactate	Glucose
Mortality (n=52)				
Median	5.80	26.69	1.65	157.50
Minimum	4.80	7.98	0.70	42.00
Maximum	11.50	62.20	8.40	421.00
Discharged (n=27)				
Median	5.60	17.14	1.40	127.00
Minimum	4.30	0.88	0.40	89.00
Maximum	11.60	45.00	4.30	309.00
Total (n=79)				
Median	5.70	20.49	1.50	143.00
Minimum	4.30	0.88	0.40	42.00
Maximum	11.60	62.20	8.40	421.00

HBA1C: hemoglobin A1C

the mortality risk 1.17 times (1.048-1.308), and a 1 g/dl increase in cortisol level increased mortality 1.08 times (1.014-1.147). HBA1C levels had no effect on mortality (p=0.166) (Table 3).

Using logistic regression analysis, we tested the impact of diabetes on mortality in 29 patients and found no significant effect of HBA1C on mortality in these patients (p=0.729). Additionally, diabetes did not significantly affect mortality in this group (p=0.156). To determine the effect of all variables (cortisol, HBA1C, APACHE II score, entry blood glucose level, lactate, age, and gender) on time spent on mechanical ventilation and ICU stay, a comprehensive model was established, which did not yield statistically significant results (p=0.090 for the number of days spent on mechanical ventilation and p=0.081 for the number of days spent in the ICU). In other words, none of the variables were found to affect the duration of stay on mechanical ventilation or in the ICU. The variables in the model

Table 3 - Effect of variables on mortality.

Variables	*P*-value	Odds ratio	95% Confidence interval	
			Lower	Upper
Cortisol	**0.017**	1.078	1.014	1.147
HBA1C	0.166	0.597	0.288	1.239
Age	0.082	1.037	0.995	1.081
Lactate	0.501	1.266	0.637	2.516
Glucose	0.439	1.005	0.993	1.017
APACHE II Score	**0.005**	1.171	1.048	1.308

APACHE: Acute Physiology And Chronic Health Evaluation, HBA1C: hemoglobin A1c

explained 20.4% of the variation in mechanical ventilation days and 20.7% of the ICU duration.

Discussion. Sepsis, trauma, burns, and any other acute illness are perceived as stress because they threaten the body's normal homeostatic processes.[5] As a protective response to stress, the adrenal cortex secretes cortisol in amounts up to 20 times higher than usual.[6] It has been argued that cortisol levels rise in correlation with the severity of acute stress. It has also been reported that cortisol values are higher in patients with lung insufficiency and sepsis than in those with gastrointestinal bleeding.[7] Furthermore, diseases that prompt rapid admission to the ICU may lead to high cortisol values, which could independently predict patient outcomes.[8-10] De Castro et al[8] shown that basal cortisol levels, measured upon admission of patients with septic shock and severe sepsis to the ICU, are the best prognostic factor for 28-day mortality. Consistent with many other studies, our research shows that mortality is associated with increased cortisol levels in patients admitted to the ICU, indicating that these levels could serve as predictive markers for high mortality.[8,11,12]

Increased cortisol due to stress stimulates hepatic gluconeogenesis and glycogenolysis. In addition, gluconeogenesis is enhanced by amino acids released from non-carbohydrate sources, such as lactate, resulting from increased protein catabolism.[13] As a result, temporary stress-induced hyperglycemia occurs as an adaptive immune–neurohormonal response to stress.[14,15] Hyperglycemia affects all major components of immunity and impairs the host's ability to fight infection, especially in hyperglycemic conditions.[16] It is well known that high blood glucose levels are associated with poor outcomes in both diabetics and non-diabetics, and is a biomarker of critical illness in patients admitted to the ICU.[17-20] Farooq et al[19] shown that hyperglycemia diagnosed during hospitalization is indicative of poor clinical outcomes and is associated with high mortality and morbidity. We found that the

glucose value measured during admission to the ICU did not affect mortality. We hypothesize that this might be attributed to the low median glucose blood level at hospitalization (143 mg/dl).

Glycosylated hemoglobin (HBA1C) is the most common marker of long-term glycoregulation, reflecting glucose levels 90 days before measurement.[21] HbA1C is said to be relatively unaffected by the acute stress response.[14] Farah et al[22] shown that HbA1C may also show changes in the inflammatory response induced by hyperglycemia, and therefore may affect morbidity and mortality in patients admitted to the ICU. In our study, we found that the HbA1C level upon admission to the ICU had no statistically significant effect on mortality and morbidity. The low and narrow range of the HbA1C values (median 5.7%) limits the ability to conclusively determine that HbA1C has no effect on mortality and morbidity. When the effect of HbA1C levels on mortality in patients with diagnosed diabetes was examined, it was not found to be substantial (p=0.729). The small number of people with diabetes included in the study may explain this (n=29).

The APACHE II score is a scoring system used to estimate the mortality risks of patients by evaluating the acute physiological and chronic health status of critically hospitalized patients. An increase of one point in this score is linked to a heightened mortality risk in hospital.[23] Consistent with the literature, in our study, an raise in the APACHE II score—which determines the severity of the disease—increased mortality.[23,24] Each point increase directly increases the risk of mortality. In our study, we found that the APACHE II score affects mortality (p=0.005) and an increase in the score by one point increases the mortality risk by 1.14. However, we found that the APACHE II score had no statistically significant effect on morbidity.

Serum lactate increases in many critical diseases due to anaerobic glycolysis.[25,26] Numerous researches have demonstrated that a high lactate level is linked to poor prognosis, emphasizing the importance of early detection in mitigating the risk of potentially poor outcomes with aggressive treatment.[27] Noparatkailas et al[28] conducted to predict 28-day mortality among patients with septic shock and severe sepsis, lactate levels higher than 2.0 mmol/L were identified as the most indicative threshold. In our study, the median lactate value of our patients was 1.5 (0.40–8.40) mmol/L. We thought that a low lactate level did not affect mortality or morbidity.

None of the variables in our study (cortisol, HBA1C, APACHE II score, entry blood glucose level, lactate, age, and gender) affected the number of days of stay on mechanical ventilation or in the ICU. This is due to the lack of significance of the model made incorporating all these variables.

Study limitations. Although the present study provides important evidences into the predictive value of cortisol and HbA1C levels for ICU mortality, several limitations should be acknowledged. First, the retrospective design restricts our capacity to determine causality between the observed biochemical markers and patient outcomes. Second, the sample size of 79 patients, although sufficient for preliminary analysis, may not capture the full variability in the population or allow robust subgroup analyses. Thirdly, the exclusion of patients on steroids or admitted for postoperative care may omit a segment of the ICU population for whom cortisol and HbA1C levels may have different implications. In addition, this study did not account for all potential confounding variables, such as variations in treatment protocols between ICUs or the presence of other comorbidities, which could influence both cortisol/HbA1C levels and patient outcomes. Future research should address these limitations by using prospective study designs, larger sample sizes, and more comprehensive assessments of biochemical markers and confounders to further elucidate the role of these biomarkers in critical care.

In conclusion, despite the limitation of a small patient cohort, our study suggests that the cortisol level at admission in intensive care could have predictive value for mortality. The HBA1C level does not affect mortality and is not accepted as a predictive value. More studies are needed to further explore and substantiate these preliminary findings.

Acknowledgment. *The authors gratefully acknowledge Scribendi (https://www.scribendi.com) for the English language editing.*

References

1. Sharma VK, Singh TG. Chronic stress and diabetes mellitus: interwoven pathologies. ***Curr Diabetes Rev*** 2020; 16: 546-556.
2. Becker CD, Sabang RL, Nogueira Cordeiro MF, Hassan IF, Goldberg MD, Scurlock CS. Hyperglycemia in medically critically ill patients: risk factors and clinical outcomes. ***Am J Med*** 2020; 133: e568-e574.
3. Stoudt K, Chawla S. Don't Sugar Coat It: Glycemic Control in the Intensive Care Unit. ***J Intensive Care Med*** 2019; 34: 889-896.
4. Tian Y, Wang R, Zhang M, Li T, He Y, Wang R. Stress-induced hyperglycemia ratio as an independent risk factor of in-hospital mortality in nonresuscitation intensive care units: a retrospective study. ***Clin Ther*** 2023; 45: 31-39.

5. Melis MJ, Miller M, Peters VBM, Singer M. The role of hormones in sepsis: an integrated overview with a focus on mitochondrial and immune cell dysfunction. ***Clin Sci (Lond)***. 2023; 137: 707-725.
6. Stamou MI, Colling C, Dichtel LE. Adrenal aging and its effects on the stress response and immunosenescence. ***Maturitas*** 2023; 168: 13-19.
7. Fowler C, Raoof N, Pastores SM. Sepsis and adrenal insufficiency. ***J Intensive Care Med*** 2023; 38: 987-996.
8. De Castro R, Ruiz D, Lavín BA, Lamsfus JA, Vazquez L, Montalban C. et al. Cortisol and adrenal androgens as independent predictors of mortality in septic patients. ***PLoS One*** 2019;14: e0214312.
9. Xu W, Qiu Y, Qiu H, Zhong M, Li L. Serum ACTH and cortisol level is associated with the acute gastrointestinal injury grade in ICU patients. ***Int J Gen Med*** 2024; 17: 127-134.
10. Bekhit OE, Mohamed SA, Yousef RM, AbdelRasol HA, Khalaf NA, Salah F. Relation between baseline total serum cortisol level and outcome in pediatric intensive care unit. ***Sci Rep*** 2019; 9: 6008.
11. Rivas M, Motes A, Ismail A, Yang S, Sotello D, Arevalo M. et al. Characteristics and outcomes of patients with sepsis who had cortisol level measurements or received hydrocortisone during their intensive care unit management: A retrospective single center study. ***SAGE Open Med*** 2023; 11: 20503121221146907.
12. Güven M, Gültekin H. Could serum total cortisol level at admission predict mortality due to coronavirus disease 2019 in the intensive care unit? A prospective study. ***Sao Paulo Med J*** 2021; 139: 398-404.
13. Holeček M. Roles of malate and aspartate in gluconeogenesis in various physiological and pathological states. ***Metabolism*** 2023; 145: 155614.
14. Furlan JC. Effects on outcomes of hyperglycemia in the hyperacute stage after acute traumatic spinal cord injury. ***Neurotrauma Rep*** 2021; 2: 14-24.
15. Zhang Z, Zhao Y, Liu Y, Wang X, Xu H, Fang Y, et al. Effect of stress-induced hyperglycemia after non-traumatic non-aneurysmal subarachnoid hemorrhage on clinical complications and functional outcomes. ***CNS Neurosci Ther*** 2022; 28: 942-952.
16. Chávez-Reyes J, Escárcega-González CE, Chavira-Suárez E, León-Buitimea A, Vázquez-León P, Morones-Ramírez J, et al. Susceptibility for some infectious diseases in patients with diabetes: the key role of glycemia. ***Front Public Health*** 2021; 9: 559595.
17. Pratiwi C, Zulkifly S, Dahlan TF, Hafidzati A, Oktavia N, Mokoagov MI, et al. Hospital related hyperglycemia as a predictor of mortality in non-diabetes patients: A systematic review. ***Diabetes Metab Syndr*** 2021; 15: 102309.
18. Zohar Y, Zilberman Itskovich S, Koren S, Zaidenstein R, Marchaim D, Koren R. The association of diabetes and hyperglycemia with sepsis outcomes: a population-based cohort analysis. ***Intern Emerg Med*** 2021; 16: 719-728.
19. Farooq N, Chuan B, Mahmud H, El Khoudary SR, Nouraie SM, Evankovich J, et al. Association of the systemic host immune response with acute hyperglycemia in mechanically ventilated septic patients. ***PLoS One*** 2021; 16: e0248853.
20. Shen H, Wang S, Zhang C, Gao W, Cui X, Zhang Q, et al. Association of hyperglycemia ratio and ventricular arrhythmia in critically ill patients admitted to the intensive care unit [published correction appears in BMC Cardiovasc Disord. 2023 May 19;23(1):260]. ***BMC Cardiovasc Disord*** 2023; 23: 215.
21. Costantini E, Carlin M, Porta M, Brizzi MF. Type 2 diabetes mellitus and sepsis: state of the art, certainties and missing evidence. ***Acta Diabetol*** 2021; 58: 1139-1151.
22. Farah R, Makhoul N, Samohvalov A, Nseir W. Plasma glycated hemoglobin a1c could predict 30-day all-cause mortality of intensive care unit patients with hyperglycemia. ***Isr Med Assoc J*** 2022; 24: 708-712.
23. Sungono V, Hariyanto H, Soesilo TEB, Adisasmita AC, Syarif S, Lukito AA, et al. Cohort study of the APACHE II score and mortality for different types of intensive care unit patients. ***Postgrad Med J*** 2022; 98: 914-918.
24. Czajka S, Ziębińska K, Marczenko K, Posmyk B, Szczepańska AJ, Krzych L. Validation of APACHE II, APACHE III and SAPS II scores in in-hospital and one year mortality prediction in a mixed intensive care unit in Poland: a cohort study. ***BMC Anesthesiol*** 2020; 20: 296.
25. Gupta GS. The lactate and the lactate dehydrogenase in inflammatory diseases and major risk factors in COVID-19 Patients. ***Inflammation*** 2022; 45: 2091-2123.
26. Rabinowitz JD, Enerbäck S. Lactate: the ugly duckling of energy metabolism. ***Nat Metab*** 2020; 2: 566-571.
27. Liu Z, Meng Z, Li Y, Zhao J, Wu S, Gou S, et al. Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with Sepsis. ***Scand J Trauma Resusc Emerg Med*** 2019; 27: 51.
28. Noparatkailas N, Inchai J, Deesomchok A. Blood lactate level and the predictor of death in non-shock septic patients. ***Indian J Crit Care Med*** 2023; 27: 93-100.